REMARKS

In the Action claims 1,4-10, 13-27, 32 and 34-40 are rejected and claims 28-31 are allowed. By this amendment claim 28 is amended to be in independent form to include the subject matter of claim 1. Thus, claim 28 and the claims depending therefrom are in condition for allowance.

The present amendment revises claim 1 to clarify the features of the invention. In particular, claim 1 is amended to recite that the visualizing step provides an indication that a predetermined temperature has been reached. Support for this feature is found on page 10 in paragraph 0020 of the specification. Claims 10, 20 and 23 are amended to correct minor clerical errors.

The pending claims in this application are claims 1, 4-10, 13-32 and 34-40 with claims 1, 10, 23 and 28 being independent. In view of these amendments, reconsideration and allowance are requested.

Rejection Under 35 USC 103(a)

Claims 1, 4-10, 13-27, 32 and 34-40 are rejected as being obvious over US Patent No. 5,935,942 to Zemer in view of US Patent No. 5,976,502 to Khoobehi and further in view of US Patent No. 3,993,754 to Rahman. The rejection is based on the position that the cited art discloses heating tissue and introducing liposomes into the body. The rejection contends that it would be obvious to modify the heating step of the primary reference according to the secondary references. For the reasons discussed herein, the proposed combination does not render the claimed invention obvious.

Zeimer either standing alone or in combination with the Khoobehi and Rahman do not suggest a method of (1) detecting a threshold temperature of the tissue, (2) hyperthermally treating tissue or (3) the step of releasing a fluorescent to provide an indication of the temperature of the tissue. The cited art also does not disclose a step of (4) heating tissue to a temperature of 45-49°C to release a dye from liposomes or (5) heating the tissue to a temperature of at least 47°C. Each step is recited in the independent claims, which is not disclosed in the cited art. The cited art also does not disclose the step of reducing the temperature of the tissue or the target site when a dye is detected as in claims 24 and 36. Thus, the claims are not obvious over the art of record.

Initially, the Action mischaracterizes the claimed invention. Page 2 of the Action states that the claims are examined "in terms of the presence of two fluorescent dyes that excite at different temperatures in the presence of a bioactive agent". The claims are clearly not limited to all of these features such the examination has unduly restricted the scope and meaning of the claims. For example, claims 1 and 10 do not recite two different dyes or a bioactive agent. More importantly, the dues do not fluoresce at different temperatures. The liposomes release the dyes at different temperatures and are fluoresced by the laser. Furthermore this disregards the claimed method steps of the invention as recited in claims 1 and 10. Independent claims 23 and 28 also do not recite a bioactive agent. Thus, the Examiner appears to have taken a very narrow interpretation of the claims.

For reasons discussed herein, the cited art either taken alone or in combination do not disclose or suggest the claimed steps of heating to thermally treat the tissue as in claims 1 and 23 or "detecting a threshold temperature" as in claim 10. Moreover, the art does not suggest heating the tissue to the claimed temperatures of at least 47° C. The invention is not just directed to a method of heating, but is also directed to a method of detecting and

visualizing a due to determine that a minimum or threshold temperature has been attained by use of the dyes that are released from liposomes. The release of the dye from the liposomes, which can then be visualized, provides a method of monitoring and detecting the temperature of the tissue. Thus, the release of the dye from the liposomes provides an indication that a temperature is attained. The release of the dye from the first liposomes provides an indication that the temperature sufficient for thermally treating the tissue is attained. The release of the dye from the second dye provides an indication that a maximum desired temperature is attained.

Claim 1 is directed to a method of introducing a liposome into the bloodstream and heating the tissue to a temperature of at least 47°C. Claim 1 is also amended to define the first liposomes as releasing the first fluorescent dye at a temperature of about 45°C to 49°C. Claim 1 further recites heating the tissue to a temperature to kill the cells and to visualize the dye as an indication that a threshold temperature has been attained to ensure that the temperature is reached for killing the cells. As noted in the specification, tissue and cell damage does not occur at 41°C as in the process disclosed in the art of record. The art of record clearly avoids extensive cell and tissue damage by heating, and thus, expressly discloses heating only to about 41°C, which is well known to be the temperature at which little or no tissue and cell damage occurs. The Action states that Zeimer heats to cause tissue damage. However, this contention is inconsistent with the Zeimer patent as a whole. The passage cited in the Action only recognizes that tissue damage can occur by heat, but provides no suggestion that the Zeimer process intends to or in fact does cause tissue damage by heating.

The Action further contends that there is no criticality of the claimed temperature range. This disregards the teachings of Zeimer and the present invention. Zeimer

specifically avoids overheating the cells to prevent tissue damage. It is well know in the art that heating above 41° C can cause tissue damage and thus the prior processes such as Zeimer expressly avoid such heating step. As set forth in the specification, the invention is directed to a process of heating to a temperature to hyperthermally treat and kill a portion of the cells. Thus, the claimed temperature is not an arbitrary temperature range as suggested in the Action. Furthermore, the temperature range is critical as recognized in the art. The cited art makes it clear that the temperature is important to the heating process and Zeimer specifically heats at a temperature to activate the drug but does heat to a temperature to hyperthermally treat the tissue and avoid killing cells. Thus, the statement in the Action that the temperature is not critical is not correct.

The temperature recited in claim 1 is well above the maximum temperature of 41° C as disclosed by Zeimer. The position in the Action that the claimed temperature of 47 C, which is 6°C higher than the highest temperature suggested by Zeimer, is an obvious modification is incorrect and contrary to the teachings of Zeimer. Zeimer provides no motivation or incentive to heat the tissue to 47°C as now claimed. The secondary references do not provide the deficiencies of Zeimer.

Claims 35-37 depend from claim 1 to recite the step of heating the tissue in the target site to 47°C to 49°C, the second dye releasing the dye at a temperature of 50°C to 60°C and reducing the temperature to 49°C or less in response to detecting the release of the second dye. The claimed temperature of 50° C to release the dye from the second liposomes and treat the tissue is clearly not suggested by Zeimer either alone or in combination with the secondary references. None of the cited art even remotely suggests heating the tissue to this temperature. It is not obvious to one of ordinary skill in the art to heat the tissue to a temperature that is above a temperature that is normally considered safe and effective. As

recognizes in the Action, Zeimer "non-invasively" heats the tissue and heats the site only to release the contents of the liposomes. Thus, Zeimer clearly does not suggest or render obvious the claimed step of heating to the claimed temperatures.

Khoobehi is cited for disclosing the use of two different liposomes containing different dyes. However, Khoobehi discloses the dyes for use in visualizing the dye in different vessels in the eye to distinguish the blood flow in the different parts of the eye. Specifically, Khoobehi used the first dye to visualize the blood flow in the retina and the second dye to visualize the blood flow in the choroid. The lasers are selected to fluoresce the selected dye in either the retina or in the choroids to be able to distinguish between the blood flows. The lasers do not hyperthermally treat the cells. The method of Khoobehi does not detect or monitor the temperature of the tissue and the method does not use the dyes to indicate that a temperature has been attained. Rahman is relevant only to the extent that it discloses the use of liposomes to release drugs. Accordingly, Khoobehi and Rahman do not provide the deficiencies of Zeimer.

Independent claim 10 is directed to a method of detecting a threshold temperature of the tissue. The method as claimed introduces the liposome into the tissue and visualizes the dye when the desired temperature has been attained. The combination of the cited art does not disclose or suggest such a method. Claim 10 recites releasing the dye at a temperature of 45°C to 49°C and heating the tissue to a temperature of 45°C. As discussed above, the art of record fails to disclose or suggest heating to these temperatures, releasing the dye at this temperature or visualizing the dye as an indicator that the desired temperature has been attained. Claim 13 is amended to recite the step of heating the target site to 47°C to 49°C as disclosed on page 11 of the specification.

The claims depending from claim 10 are also allowable for depending from an allowable base claim and for reciting additional features of the invention that are not discloses or suggested in the art of record. For example, the art does not suggest the bioactive compound of claims 14-17 in combination with the method steps of claim 10. The art also fails to disclose the heating methods of claims 18 and 19 in combination with the steps of claim 10.

Claim 20 depends from claim 10 to recite the steps of introducing a second liposome into the bloodstream where the dye is released at a temperature of at least 50°C, visualizing the dye when it is released, and "reducing" the temperature of the tissue in response o the detected second dye. This feature is clearly not disclosed or suggested in the art of record. The cited patents do not disclose or suggest reducing the temperature in response to the detection of the dye when the dye fluoresces. The Action provides no basis for the position that is it obvious to reduce the temperature of the tissue when a dye is detected.

The art of record also fails to disclose releasing the dye from the second liposome at a temperature at which denaturization occurs and then reducing the temperature below the denaturization temperature as in claim 21, or heating to a temperature below the denaturization temperature and below the temperature where the second dye is released as in claim 22. Accordingly, these claims are not obvious over the cited art.

Independent claim 23 is directed to a method of hyperthermally treating tissue by introducing a first and second liposome into the blood stream where the first liposome releases the dye at a temperature of 45-49°C and the second liposome releases the dye at a temperature of 50°C. Claim 23 also recited heating the target site to release the first liposome without releasing the second liposome. The cited art does not suggest heating to release only one of the dyes. The cited art provides no motivation or incentive to carry out the claimed

steps. Furthermore, the Action does discuss this feature or provide a basis for the position that the claimed steps are obvious over the art. The art does not suggest the claimed temperatures or the step of releasing one of the dyes at a temperature of 45-49°C and also heating to a temperature without releasing the dye from the second liposome. Accordingly, claim 23 and the claims depending therefrom are allowable over the art of record.

Claim 24 depends from claim 23 to recite the step of monitoring and detecting the fluorescence of the second dye and reducing the temperature of the tissue below the denaturing temperature in response to the detection of the second dye. The art does not disclose or suggest these features of the claimed invention.

The features of the claims depending from claim 23 are also not disclosed or suggested in the art. For example, the art fails to disclose the different colored dye of claim 25, the liposomes of claim 26 or the liposome having a release temperature of 50-60°C in combination with the steps of claim 23. The art also fails to disclose heating the tissue to a temperature below the release temperature of the second liposomes as in claim 39 or reducing the temperature of the tissue when the second dye is released and detected as in claim 40.

For the reasons discussed above, the art of record does not disclose or suggest the features of the claimed process. Accordingly, the claims are submitted to be in condition for allowance. Reconsideration and allowance are requested.

Respectfully submitted,

November 26, 2004

Garrett V. Davis
Reg. No. 32,023

Roylance, Abrams, Berdo & Goodman, L.L.P.
1300 19th Street, N.W., Suite 600
Washington, D.C. 20036
(202) 659-9076